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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/598,117	HARRIS, CRAIG STEVEN	
	Examiner	Art Unit	
	CRAIG RICCI	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *1,4,12 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-3, 5-11, 13-14, 16 and 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/15/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-16 and 19-20 are currently pending. Claims 1, 4, 12 and 15 are withdrawn. Claims 17-18 are cancelled. Accordingly, claims 2-3, 5-11, 13-14, 16 and 19-20 are the subject of this Office Action. This is the first Office Action on the merits of the claims.

Information Disclosure Statement

2. All references have been considered.

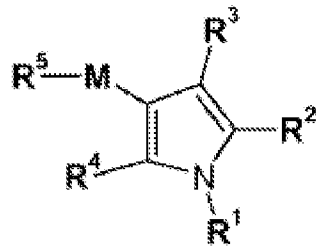
Priority

3. The earliest effective filing date afforded the instantly claimed invention has been determined to be 02/17/2005 as to claims 2-3, 5-11, 13-14, 16 and 19-20.

4. Acknowledgment is made of Applicant's claim for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on a prior application filed in Europe on 02/20/2004. The certified copy has been filed in parent Application No. PCT/GB05/00560, filed on 02/17/2005.

Election/Restrictions

Applicant's election with traverse of Group V in the reply filed on 09/23/2008 is acknowledged. Applicant traverses on the ground that *Kawai et al* (WO 98/02430) does not anticipate the instant invention for purposes of breaking unity because of the fact that a mere overlapping generic disclosure is not anticipatory. Examiner agrees that mere overlapping generic disclosure is not anticipatory. However, the instant application is drawn to compounds having a generic pyrrole core of the formula



wherein the variable groups R^1-R^5 and M are defined in the claim. Significantly for each variable group R^1-R^5 and M there are numerous possible options, including the possibility that each variable group can include additional variable groups which further can include even more variable groups and so on. Accordingly it is clear that the generic formula above encompasses literally millions of potential compound species, each having distinct structural attributes. For example, as recited by instant claim 2, R^5 can be formula III-o wherein Q is a direct bond such that R^5 is simply a heterocycle whereas R^5 can also be formula III-m, $-N(R^{16})C(=O)N(R^{14})(R^{15})$ wherein R^{14}-R^{16} can be any number of possible substituents. Clearly two compounds based on these two distinct possibilities of R^5 would possess distinct structural attributes. Yet, the claims provide for innumerous additional possibilites. Since it is evident that none of the structural features based on the possible variable groups necessarily overlaps, the only special technical feature shared between the millions of potential compounds encompassed by the claims as recited is their pyrrole core. And furthermore, the pyrrole core of claim 1 does not present a contribution over the prior art. As disclosed in *Kawai et al* (WO 98/02430) (abstract) provided by Applicant, the pyrrole core of instant claim 1 is anticipated. As such, it can not be maintained that each of the compounds encompassed by the claims share a special technical feature.

Therefore, the claims are not so linked within the meaning of PCT Rule 13.2 so as to form a single inventive concept, and unity between is broken.

5. Applicant has further suggested a restriction group wherein R^2 is optionally substituted phenyl (rather than wherein R^2 is 3,5-dimethylphenyl); wherein M is –CH2-CH2- or CH=CH; and wherein R^5 contains a gem-dimethyl group adjacent to the M group. Examiner agrees to remove the requirement that R^2 is 3,5-dimethylphenyl and instead accepts that R^2 is optionally substituted phenyl. Applicant's other suggestions are already encompassed by the elected Group.

6. The restriction is thus made FINAL.

7. The elected species read upon claims 2-3, 5-11, 13-14, 16 and 19-20. Applicant timely traversed the restriction (election) requirement in the reply filed on 09/23/2008.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **Claims 2-3, 5-11, 13, 16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds**.

10. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)).

These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

11. Nature of the invention: Claims 2-3, 5-11, 13, 16 and 19-20 are drawn to compounds and pharmaceutical compositions comprising a compound of Formula (I) as well as salts, solvates and prodrugs thereof. For a compound to be a prodrug, it must meet three tests: first, it must itself be biologically inactive; second, it must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration; and third, that second substance must be clinically effective. Finding a prodrug is an empirical exercise and determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. For example, predicting if a certain ester of a claimed alcohol is in fact a prodrug that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science.

12. Breadth of the claims: The claim encompasses not only the compound of Formula (I), but also the presently unknown list of potential prodrugs of the compound of Formula (I). Accordingly, the claim encompasses hundreds of thousands of compositions.

13. Guidance of the specification/The existence of working examples: The direction concerning the prodrugs is not found in the specification and there are no working examples of a prodrug of a compound of Formula (I).

14. State of the art/Predictability of the art: *Wolff, Manfred E* ((Burger's Medicinal Chemistry 5ed, Part I) John Wiley & Sons, 1995, pages 975-977) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

15. *Wolff* also summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Furthermore, *Banker* ((Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596) in the first sentence, third paragraph on page 596, states that "extensive development must be undertaken" to find a prodrug.

16. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h)

17. Amount of experimentation necessary: MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of unknown structure is, in fact, a prodrug.

18. **Claims 2-3, 5-11, 13, 16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds**.

19. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

20. Nature of the invention: Claims 2-3, 5-11, 13, 16 and 19-20 are drawn to compounds and pharmaceutical compositions comprising a compound of Formula (I) as well as salts, solvates and prodrugs thereof.

21. Breadth of the claims: The claim encompasses not only the compound of Formula (I), but also the presently unknown list of potential solvates of the compound of Formula (I). Accordingly, the claim encompasses hundreds of thousands of compositions.

22. Guidance of the specification/The existence of working examples: The direction concerning the solvates is not found in the specification and there are no working examples of a solvate of a compound of Formula (I).

23. State of the art/Predictability of the art: Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physiochemical properties that can profoundly influence the bioavailability, manufacturability, purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

24. For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However,

the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. There fore, for these reasons, the state of the prior art is one of unpredictability.

25. As stated above, crystalline solids can exist in the form of polymorph, solvates, or hydrates. As stated by *Vippagunta et al*, "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the intial stages of the drug development" (abstract). Furthermore, *Vippagunta et al* disclose that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (Page 18, Section 3.4).

26. Amount of experimentation necessary: MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention

without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. It would require undue experimentation to prepare any solvate of the compounds of Formula (I). The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

27. **Claims 2-3, 5-11, 13, 16 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some compound species, does not reasonably provide enablement for all compounds as claimed**.

28. Specifically, claims 2 and 19 recite compounds having the formula (I) wherein:

A is selected from:

(i) a direct bond;

(ii) optionally substituted C_{1-6}alkylene wherein the optional substituents are independently selected from: hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, aryl or arylC_{1-6}alkyl;

(iii) a carbocyclic ring of 3-7 atoms;

(iv) a carbonyl group or –C(O)–C($\mathbf{R^d}\mathbf{R^d}$)-, wherein $\mathbf{R^d}$ is independently selected from hydrogen and C_{1-6}alkyl;

K is selected from: a direct bond, -$(CH_2)_{s1}$-, -$(CH_2)_{s1}$-O-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-C(O)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-S(O_n)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R^{17a}}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-C(O)N($\mathbf{R^{17a}}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R^{17a}}$)C(O)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R^{17a}}$)C(O)N($\mathbf{R^{17a}}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-OC(O)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-C(O)O-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-N($\mathbf{R^{17a}}$)C(O)O-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-OC(O)N($\mathbf{R^{17a}}$)-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-OS(O_n)-$(CH_2)_{s2}$-, or -$(CH_2)_{s1}$-S(O_n)-O-$(CH_2)_{s2}$-, -$(CH_2)_{s1}$-S(O)$_2$N($\mathbf{R^{17a}}$)-$(CH_2)_{s2}$-or -$(CH_2)_{s1}$-N($\mathbf{R^{17a}}$)S(O)$_2$-$(CH_2)_{s2}$-; wherein the -$(CH_2)_{s1}$- and -$(CH_2)_{s2}$- groups are independently optionally substituted by hydroxy or C_{1-4}alkyl and wherein when s1>1 or s2>1 then the CH_2 group can optionally be a branched chain.;

and

R^8 is selected from:

(i) hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, hydroxy, hydroxyC_{1-6}alkyl, cyano, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, C_{1-6}alkyl-$S(O_n)$-, -O-**R^b**, -N**R^bR^c**, -C(O)-**R^b**, -C(O)O-**R^b**, -CON**R^bR^c**, NH-C(O)-**R^b** or $-S(O_n)N$**R^bR^c**,**

where **R^b** and **R^c** are independently selected from hydrogen and C_{1-6}alkyl optionally substituted with hydroxy, amino, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, HO-C_{2-4}alkyl-NH- or HO-C_{2-4}alkyl-N(C_{1-4}alkyl)-;

(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) carbocyclyl (such as C_{3-7}cycloalkyl or aryl) or arylC_{1-6}alkyl each of which is optionally substituted by **R^{12}**, or **R^{13}**;

(iv) heterocyclyl or heterocyclylC_{1-6}alkyl each of which is optionally substituted by up to 4 substituents independently selected from **R^{12}** or **R^{13}**, and where any nitrogen atoms within a heterocyclyl group are, where chemically allowed, optionally in their oxidised (N→O, N-OH) state;

although in claim 19, variable group R^8 does not include group (ii).

29. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification only enables compounds wherein A is (ii); wherein K is $-(CH_2)_{s1}-$ or $-(CH_2)_{s1}-C(O)-(CH_2)_{s2}-$; and wherein R^8 is (iv).

30. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered, with the most relevant factors discussed below.

31. Nature of the invention: The rejected claims are drawn to compounds that are antagonists of gonadotropin releasing hormone (GnRH) activity (Specification, Page 1).

It is well known and one of ordinary skill in the art would appreciate that the development of effective antagonists is complicated. Accordingly, the nature of the invention is one of extreme complexity.

32. Breadth of the claims: The claims are drawn to a number of compounds that are alleged to antagonize the GnRH activity. As drafted, the claim encompasses thousands of compounds. The broadness of the claims exacerbates the complexity of the invention, since it implies that each compound having distinct substituents is capable of performing the same complex task; namely, antagonizing the GnRH activity.

33. Guidance of the specification/The existence of working examples: As evidence of the thousands of claimed compounds, Applicant provides only 12 examples. However, none of the disclosed compounds contain A where A is anything except unsubstituted C_1 alkylene; K wherein K is anything except CH_2, -(CH_2)-C(O), or C(O); and R^8 wherein R^8 is anything except heterocycle. Additionally, Applicant does not disclose any structure activity relationship studies or potency data that would suggest to one of ordinary skill in the art the pharmacokinetic properties of the disclosed examples or provide guidance to the prophetic substituents.

34. State of the art/Predictability of the art: As discussed above, the state of the art is highly complex. As evidenced by *Arnould et al* (Bioorg Med Chem Lett 17:6448-6454, 2007) various substitutions at specific positions of structurally and functionally related compounds significantly altered the compound's potency. Specifically, *Arnould et al* teach that the modification of structurally related GnRH antagonists at K and R^8 (as defined in the instant invention, defined as NR^1 in *Arnould et al*) dramatically altered the

IC50 of the compound (Page 6451, Table 2). Accordingly, the state of the art is one of extreme complexity and unpredictability, and one of ordinary skill in the art would not reasonably be able predict whether any of the thousands of compounds encompassed by the instant claims would have utility.

35. Amount of experimentation necessary: Given the complexity of the invention, which is exacerbated by the enormous scope of the claims, given the unpredictability of the art, and further given the paucity of examples including the lack of concrete examples of various claimed permutations and the complete lack of guidance by the Applicant, it would require undue experimentation by one of ordinary skill in the art to practice the invention as claimed. Specifically, one of ordinary skill in the art would be required to produce each of the numerous compounds encompassed by the instant claims and then individually evaluate their potency.

Claim Rejections - 35 USC § 103

36. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

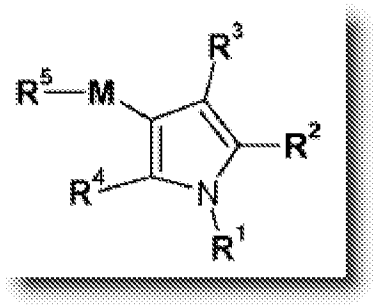
37. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

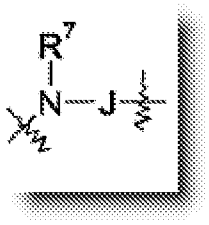
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

38. **Claims 2-3, 5-11, 13-14, 16 and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Bird et al* (WO 2004/017961) in view of *Williams et al* (Foye's Priciples of Medicinal Chemistry, Lippincott Williams and Wilkins, 2002, pages 59-61), *Walsh et al* (WO 2000/053602), and *Goulet et al* (WO 2000/69433)**.

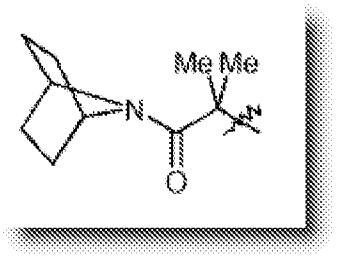
39. Instant claim 2 is drawn to compounds which are alleged gonadotrophin releasing hormone antagonists having the following generic structure



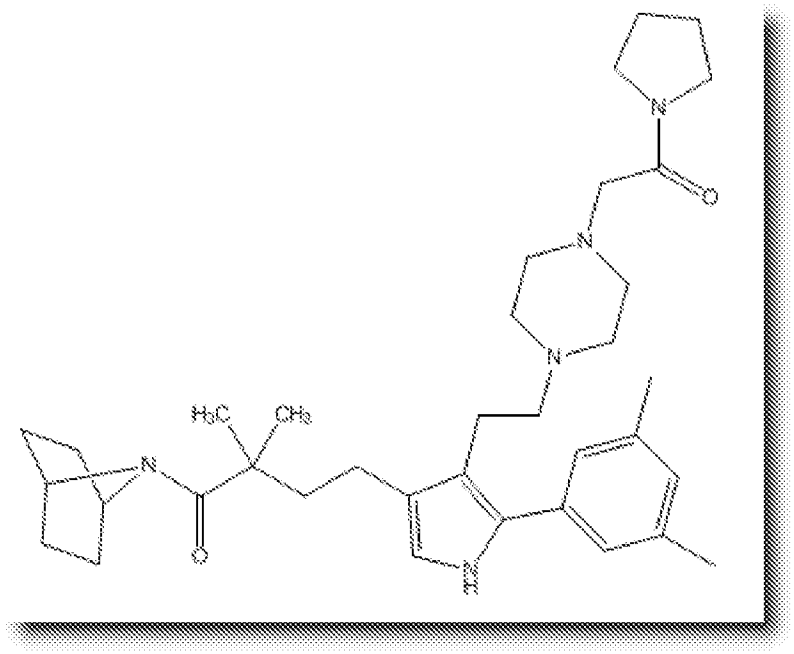
wherein R^2 is optionally substituted phenyl; R^3 is Formula

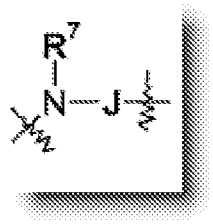
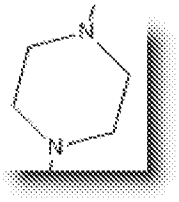
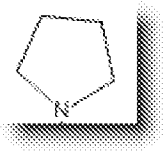


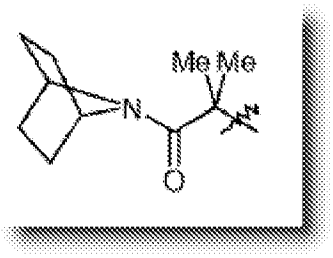
(IIc) or (IId); the group together forms an optionally substituted



heterocyclic ring; and R^5 is . Accordingly, the compounds of claim 1 encompass the following compound species

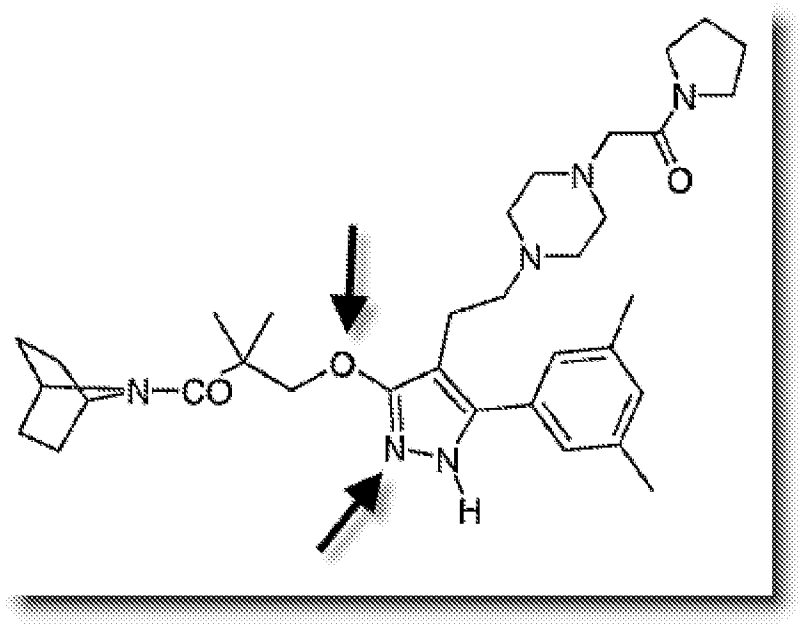


(Specification Page 67, Example 4) wherein R^1 is hydrogen; R^2 is 3,5-dimethylphenyl; R^3 is Formula (IId) wherein R^6 and R^{6a} are hydrogen, A is optionally substituted C_{1-5} alkylene (more specifically C_1 alkylene),  forms an optionally substituted heterocyclic ring (more specifically ), K is $–(CH_2)_{s1}\text{-}C(O)\text{-}(CH_2)_{s2}$- wherein s1 is 1 and s2 is 0, and wherein R^8 is a heterocycle (more specifically ); R^4 is hydrogen; M is



CH_2- CH_2; and R^5 is . Furthermore, the above compound reads on claims 2-3, 5-11, 13-14, and 19.

40. *Bird et al* teach compounds which are gonadotrophin releasing hormone antagonists having the following structure



which is identical to the compound taught by the instant application except as indicated by arrows. Specifically, whereas the instant claims are drawn to compounds containing a pyrrole core and wherein M is CH_2-CH_2, *Bird et al* teach structurally and functionally related compounds having a pyrazole core and wherein M is O- CH_2. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute –CH= (in the instant application) for –N= (as taught by *Bird et al*) and furthermore it would

have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute - CH_2 (as taught by the instant application) for –O (as taught by *Bird et al*) for the following reasons:

41. **FIRST**, as taught by *Williams et al* "When a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate… The medicinal chemist therefore must modify the compound to reduce or eliminate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as isosteric or bioisosteric replacement" (Page 59). Although it is clear that "the use of bioisosteric replacement (classical or nonclassical) in drug development is highly dependent upon the biological system being investigated" and that "No hard and fast rules exist to determine what bioisosteric replacement is going to work with a given molecule" it is also clear that "some generalizations have been possible" (Page 60). Notably, one such generalization is that -CH_2 and –O (which are classic bivalent biosteric groups) and –CH= and –N= (which are classic trivalent biosteric groups) can replace each other (Page 61, Table 2.9). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to replace the bivalent oxygen and trivalent nitrogen atoms taught by *Bird et al* with the bivalent methylene and trivalent –CH= groups as recited by the instant claims. The person of ordinary skill in the art at the time the invention was made would have been motivated to make the bioisosteric

modifications to synthesize similar compounds that retain biological activity, but have improved physiochemical properties and better pharmacokinetic behavior.

42. And **SECOND**, while it is clear that "the use of bioisosteric replacement (classical or nonclassical) in drug development is highly dependent upon the biological system being investigated" and that "No hard and fast rules exist to determine what bioisosteric replacement is going to work with a given molecule" (Page 60) as discussed above, in the case of the instant compound, a person of ordinary skill in the art at the time the invention was made would have predicted that the bioisosteric modifications would provide a reasonable expectation of achieving the desired results since (1) as taught generically by *Bird et al*, M can be $-(CH_2)_{0-2}-O-$ or -C(O)NH- which would suggest to the person of ordinary skill in the art at the time the invention was made that modification of M would be feasible; and (2) *Walsh et al* (Page 41, Example 1) and *Goulet et al* (Page 48, Example 2) teach that structurally related compounds having distinct core rings (i.e., different from the pyrazole core ring taught by *Bird et al* and different from the pyrrole core ring of the instant compound) are useful as gonadotrophin releasing hormone antagonists. Thus, a person of ordinary skill in the art at the time the invention was made would have predicted that modification of the core ring in otherwise structurally related compounds would provide compounds with similar biological activities.

43. As stated by MPEP 2144.09:

> A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979).

In the instant case, the compounds taught by *Bird et al* are structurally and functionally similar. Furthermore, the only differences are classic bioisosteric modifications that a person of ordinary skill in the art would have been motivated to make in view of *Williams et al*, *Walsh et al*, and *Goulet et al*. Accordingly, claims 2-3, 5-11, 13-14, and 19 are rejected as *prima facie* obvious.

44. Instant claims 16 and 20 are drawn to a pharmaceutical formulation comprising the compounds of claim 2 and 19, respectively. As stated by *Bird et al*, the compounds of the invention "can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier" (Page 136, Lines 26-27).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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